



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2014

Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial

Klamroth-Marganska, Verena ; Blanco, Javier ; Campen, Katrin ; Curt, Armin ; Dietz, Volker ; Ettlin, Thierry ; Felder, Morena ; Fellinghauer, Bernd ; Guidali, Marco ; Kollmar, Anja ; Luft, Andreas ; Nef, Tobias ; Schuster-Amft, Corina ; Stahel, Werner ; Riener, Robert

DOI: [https://doi.org/10.1016/S1474-4422\(13\)70305-3](https://doi.org/10.1016/S1474-4422(13)70305-3)

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-88799>

Journal Article

Accepted Version

Originally published at:

Klamroth-Marganska, Verena; Blanco, Javier; Campen, Katrin; Curt, Armin; Dietz, Volker; Ettlin, Thierry; Felder, Morena; Fellinghauer, Bernd; Guidali, Marco; Kollmar, Anja; Luft, Andreas; Nef, Tobias; Schuster-Amft, Corina; Stahel, Werner; Riener, Robert (2014). Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. *Lancet Neurology*, 13(2):159-166.

DOI: [https://doi.org/10.1016/S1474-4422\(13\)70305-3](https://doi.org/10.1016/S1474-4422(13)70305-3)

Three-dimensional, task-specific robot therapy of the arm: a multicenter randomized clinical trial in stroke patients

Verena Klamroth-Marganska MD^{1,2}, Javier Blanco MD³, Katrin Campen⁴, Armin Curt MD², Volker Dietz MD², Thierry Ettlin⁵, Morena Felder MD³, Bernd Fellinghauer PhD⁶, Marco Guidali PhD^{1,2}, Anja Kollmar^{1,2}, Andreas Luft MD^{4,7}, Tobias Nef PhD⁸, Corina Schuster-Amft PhD^{5,9}, Werner Stahel PhD⁶, Robert Riener MD^{1,2}

¹Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland.

²Spinal Cord Injury Center, University Hospital Balgrist, University of Zurich, Zurich, Switzerland.

³Zürcher Höhenkliniken, Wald, Switzerland.

⁴Zentrum für Ambulante Rehabilitation ZAR, Zurich, Switzerland.

⁵Reha Rheinfelden, Rheinfelden, Switzerland.

⁶Seminar for Statistics, ETH Zurich, Switzerland.

⁷Clinical Neurorehabilitation, Department of Neurology, University of Zurich, Zurich, Switzerland.

⁸ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, University of Bern, Bern, Switzerland.

⁹Institute for Rehabilitation and Performance Technology, Bern University of Applied Sciences, Burgdorf, Switzerland.

Abstract

Background: Arm hemiparesis, secondary to stroke, is common and disabling. The robot ARMin, which is designed for neurorehabilitation of the arm, allows for task-specific training in a 3-dimensional workspace. The authors assessed whether ARMin reduces impairment and enhances arm motor function of the paretic arm more effectively than conventional therapy. **Methods:** Using a prospective, multicenter (four centers in Switzerland), controlled, parallel-group, single-blind (examiner-blind) demonstration-of-concept study (phase II/stage 3), chronic (more than six months) post-stroke subjects with moderate to severe impairment of an arm, received either neurorehabilitative therapy with ARMin or conventional therapy comprising physical or occupational therapy. The therapy in both groups was given three times per week for eight weeks resulting in 24 therapy sessions on the whole. Each session lasted one hour. A battery of assessments was performed at five time points (t0: before therapy, t1: after four weeks of therapy, t2: at the end of therapy (after 8 weeks), t3: at 16 weeks follow-up, and t4 at 34 weeks follow-up). Primary outcome for evaluating motor function was the change in the impairment-based test, FMA-UE (Fugl-Meyer Assessment of the upper extremity motor function) over the course of the study. **Results:** Out of 77 subjects, 73 completed the study; among them, 38 were enrolled to robotic therapy with ARMin and 35 to conventional therapy. Robotic training of the affected arm with ARMin was found to be more effective than conventional therapy in terms of motor function (FMA-UE: $F = 4.1$, $p = 0.041$, mean difference: 0.78 points, confidence interval [0.03 - 1.53]). No major adverse events related to the study occurred.

Interpretation: Neurorehabilitative therapy using task-oriented training with an exoskeleton robot can enhance improvement of the paretic arm even in the chronic state after stroke reducing arm impairment more effectively than conventional therapy. However, superiority is based on small

24 absolute differences and weak significance which leave the clinical relevance and evidence in
25 question. Therapy was shown to be safe.

26 **Funding:** Swiss National Science Foundation (Nr.325230-120621) and Bangerter-Rhyner Stiftung
27 (project: ARMin).

28 Keywords: robotics, exoskeleton, upper limb, arm training, hemiparesis, task-oriented training,
29 neurorehabilitation, stroke, randomized clinical trial

30

31

32 **Introduction**

33 Despite preventive measures, stroke remains a leading cause of permanent disability around the
34 world [4]. On average, every 40 seconds a subject in the U.S. suffers a stroke [5], and 30% to 66% of
35 the survivors suffer from long-term loss of arm function [6]. As conventional therapeutic approaches
36 for functional rehabilitation after stroke show limited effectiveness [7], robotic approaches are
37 increasingly being subjected to scientific scrutiny [8]. A Cochrane meta-analysis [9] compared the
38 efficacy of robotic devices to other therapeutic interventions in treating motor dysfunction after
39 stroke. Results show that paretic arm function and activities of daily living (ADL) may improve with
40 these devices, but not arm muscle strength. It is of debate whether dose accounts for the
41 effectiveness of robot-assisted therapy [10-12]. Robotic devices allow for further modes of therapy
42 that cannot be accomplished with conventional therapy methods, such as adaptive training [13], or
43 highly repetitive, complex movements [14]. The devices that were tested in the Cochrane meta-
44 analysis [9] mainly support single joints or allow for planar movements only [12, 15]. The exoskeleton
45 robot ARMin (Figure 1, [16]) features a large range of motions in the 3-dimensional space; it provides
46 intensive and task-specific training strategies for the arm which have been identified to be
47 particularly effective in promoting motor function [17-20]. With seven degrees of freedom, ARMin
48 supports the physiological movements of the shoulder and arm, as well as opening and closing of the
49 hand. A teach-and-repeat procedure is implemented, where the therapist can mobilize the patient's
50 arm on an arbitrary, patient-individual trajectory, while the robot actively compensates friction and
51 gravity [16]. A battery of games and activities of daily living (ADL) can be practiced in a virtual reality
52 environment. They include ball games, a labyrinth game and different kitchen activities [14].
53 Audiovisual cues and online information about performance are provided to increase motivation.
54 Within the ADL tasks and games, the patient moves his arm in a virtual tunnel (patient-cooperative

55 path controller [14]). Parameters such as difficulty, speed, tunnel width, and gravitational and
56 movement assistances are adjusted by the therapist.

57 The main question addressed in the present study is whether robotic training of the affected arm
58 with ARMin reduces motor impairment with respect to arm and hand function more effectively than
59 conventional therapy. As primary outcome, changes in motor function over the course of the study
60 were measured by means of the upper-limb portion of the Fugl-Meyer assessment (FMA-UE).
61 Furthermore, we investigated whether robotic therapy with ARMin had long-term effects on
62 impairment, activity and participation, and which subpopulations (stratified by time gap since stroke,
63 severity, age, hand dominance) benefit most from the interventions.

64 **Methods**

65 Study design and participants

66 This study was a prospective, multicenter, parallel-group designed trial. Randomization was
67 performed by an independent person not involved in the study. All assessors (N=5) were blinded for
68 treatment allocation. It was designed to act as a demonstration of concept trial testing the safety and
69 developing preliminary efficacy data (phase II/stage 3, according to Dobkin [21]). Participants after
70 first-ever cerebrovascular accident (CVA) were randomly assigned to robotic or conventional therapy.
71 Four clinical centers in Switzerland (Uniklinik Balgrist UKB, Reha Rheinfelden RRh, Zentrum für
72 Ambulante Rehabilitation Zürich ZAR, Zürcher Höhenklinik Wald ZHW) were involved in recruitment
73 and therapy. ZHW and RRh are neurorehabilitation centers in the agglomeration of Zurich and Basel
74 with a catchment area of approximately 1.2 million individuals. Through inpatient and outpatient
75 facilities, each center treats between 300 and 600 subjects after CVA annually. ZAR is an outpatient
76 clinic for neurorehabilitation situated in Zurich with more than 100 subjects after CVA per year
77 treated. UKB is the clinical partner for technical development of the ARMin robot and situated in
78 Zurich. All the participating centers are experienced in clinical research projects.

79 Subjects were recruited through the centers and media during the course of the study. They were
80 considered eligible if they were diagnosed with a single CVA in the chronic state (minimum six
81 months) with moderate to severe arm paresis (8 to 38 points of the FMA-UE). To approve chronic
82 state post-stroke, the FMA-UE was repeated after three to four weeks (t0) and a difference of up to 3
83 points was accepted for inclusion (see Table 1 for further eligibility criteria). Written informed
84 consent was obtained from each participant prior to enrollment.

85 Because of difficulties in enrolling the intended number of subjects, the study was prolonged for 17
86 months and the eligibility criteria were widened 19 months after start of the study, as follows: The
87 criterion “ischemic stroke” was extended to “CVA”; the exclusion criterion “epilepsy” was discarded
88 and the age restriction changed from “18 to 80 years” to “minimum 18 years”. Subjects who had not
89 been originally considered or rejected, due to these eligibility criteria, were contacted and testing for
90 eligibility was offered. Because of recruitment difficulties at one center, five allocation envelopes
91 were transferred from there to another center to treat five additional participants at the latter.

92 Procedures

93 Therapy of both groups (robotic and conventional therapy) was applied in the centers for a period of
94 eight weeks, three times weekly (total 24 sessions). Only one session per day was scheduled. Missed
95 sessions (up to four) could be rescheduled if training duration did not exceed nine weeks. Minimal
96 time for therapy (excluding time for preparation, diagnostics, documentation etc.) for both groups
97 was 45 minutes.

98 During the robotic therapy with ARMin, each of the three therapy modes (mobilization, games, and
99 ADL training) had to be performed for a minimum of ten minutes each. The control group received
100 “conventional therapy”: the term denotes the common neurorehabilitation treatment applied to
101 stroke patients in outpatient facilities, namely occupational therapy or physiotherapy. Therapists

102 were asked to perform a regular therapy usually including mobilization, games and/or ADL. Only
103 restriction was not to use automated technical devices that might be available in therapy settings.

104 The same occupational and physical therapists conducted both training forms (robotic and
105 conventional therapy) and were assigned to the individual participant prior to the allocation of
106 therapy type. Therapists had more than four years of professional experience. At two centers an
107 occupational therapist, at one center a physical therapist, and at one center a physical and an
108 occupational therapist were involved, but each participant was treated by the same person (each
109 with a substitute). Each therapist received several hours of teaching in robotic therapy by an
110 instructed therapist and the responsible engineer (one-to-one-training, observation at therapies,
111 supervised training).

112 Primary outcome was the change in FMA-UE score. The motor impairment test involves 33 items,
113 which assess voluntary movement, reflex activity, grasp, and coordination on an ordinal scale (0-1-2),
114 with a total score of 0 ("no function") to 66 points ("normal function") [22]. The threshold for the
115 minimal clinically important difference (MCID) in chronic subjects with minimal to moderate
116 impairment after stroke is about 5 points (4.25 to 7.25 points [23]) and the minimal detectable
117 change (MDC95) is 8% or 5.2 points [24, 25].

118 Secondary outcome measures included the Wolf Motor Function test (WMFT), a disability-based test
119 of 15 tasks, that assesses the quality (WMFT_i: 0 = "does not attempt with the involved arm" to 5 =
120 "affected arm does participate; movement appears to be normal") and time (WMFT_t: max. 120
121 seconds) of task performance [26, 27]. Six tasks relate to joint-segment movements and nine tasks to
122 integrative functional movements. In addition, grip strength is measured with a handheld
123 dynamometer (Jamar). Following were the other secondary outcome measures: i) the quality of
124 movement section of the Motor Activity Log (MAL-QOM,[28]), a semistructured interview with 30
125 questions that evaluate the use of the paretic arm and hand during ADL with a rank order scale (0-5),

126 ii) the Stroke Impact Scale version 2.0 (SIS, [29]), a self-report questionnaire composed of 60 items
127 that investigate changes in nine domains, comprising impairment, disability, and handicap (SIS: total
128 score; physical domain SIS_{pd}: combination of the four domains strength, hand function, mobility and
129 ADL), iii) the Goal Attainment Scale (GAS, [30]), a measure of goals that could be achieved with the
130 intervention (two goals were defined by the therapist together with the patient in the first therapy
131 session; the achievement at the last session was measured on a 5-point scale ranging from -2 to +2
132 and then averaged), iv) the modified Ashworth Scale (mAS, [31]), a test of resistance to passive joint
133 movement (we averaged the mAS values from the following nine single joint movements: flexion and
134 extension of elbow, wrist, finger, thumb; and flexion of the shoulder), and v) mean strength
135 measured by ARMin (the subject's arm is brought to predefined positions and the subject applies
136 maximal, voluntary, isometric torques in directions of shoulder
137 abduction/adduction/anteversion/retroversion and elbow flexion/extension; peak torques are
138 derived from the measured counter-steering motor currents, and the mean strength in Newtonmeter
139 calculated).

140 Evaluators included a physician in training and occupational therapists or physiotherapists, all blinded
141 to group assignment. They were first instructed by a therapist at ETH Zurich to ensure
142 standardization. Instruction included a theoretical and practical education program and supervised
143 practice on subjects. Evaluators performed battery testing at six time-points: three to four weeks
144 before assignment (tm1), immediately before therapy (t0), 4-weeks interim therapy (t1), at the end
145 of 8-weeks therapy (t2), and at 16-week (t3) and 34-week follow-ups (t4) (see Figure 1). Only those
146 subjects who fulfilled all the eligibility criteria at t0 were included.

147 Data management and monitoring, and administration were controlled by the study coordinator. The
148 principal investigators of each of the clinical centers approved all decisions and met annually to
149 assure conductance according to the protocol. The study procedures were approved by the

150 respective institutional review boards of each participating center (Cantonal Ethical Committees).
151 The study was registered on ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT00719433).

152

153 ***Randomization and Masking***

154 We used a center-stratified randomization procedure with one block for each center and a
155 proportion of 1:1 for robotic to conventional therapy. A computer-generated list of random numbers
156 [32] which pair both a unique sequential number and the treatment type (robotic/conventional) was
157 used. Pairs were sealed in tamper-evident envelopes by the study coordinator. Subjects drew lots
158 which were presented by a person not involved in testing. The assignment to an occupational or
159 physiotherapist was not randomized but determined by the available clinical staff on site. Evaluators
160 were blinded to treatment allocation and the clinical tests FMA-UE and WMFT were video-taped for
161 later control.

162 Clinical centers and group assignment were coded during data processing. In this way, we aimed to
163 avoid bias in reporting, data processing and data analysis. For each participant, all recorded data
164 were cross-checked by a study nurse not involved in data collection.

165

166 **Statistical Analysis**

167 The calculation of the sample size was based on the data of the FMA-UE of a comparable study [33]
168 that assessed the effects of robot-assisted training and conventional therapy in 27 chronic stroke
169 patients. After two months of training, an average improvement in the FMA-UE score of 4.7 and 3.1
170 points, respectively, was found. The largest standard deviation (SD) was 2.5 points. Assuming $\alpha < 0.05$
171 when tested two-tailed and a requested power of 80% a target sample size of 80 participants was

172 needed for the trial [34]. Expecting a drop out of 10%, we chose a sample size of 44 participants for
173 each group, which resulted in a final target size of 88.

174 A significance level of 0.05 was defined for all the analyses. A repeated measures linear mixed model
175 was used to assess the effect of treatment over the entire course of the study for each of the
176 outcome measures. In each model, group (ARMin, control) was used as the between-subjects factor,
177 baseline function (baseline value at t0), and time gap since stroke (in months) as covariates, and
178 center (centers 1, 2, 3, 4) as random effect. The model assumptions were checked using Tukey-
179 Anscombe residual plots and quantile-quantile (QQ) plots. The secondary outcome GAS was only
180 assessed at a single time point (t2). As such, a univariate ANOVA with the same model term structure
181 was used. All calculations were performed using IBM SPSS 20.

182 During the process of data analysis, we decided to perform hypothesis generating post-hoc subgroup
183 analyses. The subjects were divided based on median splits for “time gap since stroke”, “age”, “hand
184 dominance”, and “severity” (FMA-UE at t0) in the linear mixed model.

185 According to “intention-to-treat” analysis, all assigned participants were analyzed after their initial
186 entry check regardless of a) their adherence with the entry criteria b) the treatment they received
187 and c) a deviation from the protocol [35]. A modified application of the intention-to-treat was
188 followed, meaning that subjects were only included when outcome data from follow-up assessments
189 were available for the randomized subjects. For missing data, the last observation was carried
190 forward or, if no former observation was applicable, the next observation carried backward [36].

191

192 ***Role of the funding source***

193 The corresponding author has final responsibility for the decision to submit for publication. All
194 authors had full access to all of the data in the study.

195 Funding sources were the Swiss National Science Foundation and the Bangerter-Rhyner Foundation.
196 They were neither involved in the study design nor in the collection, analysis, and interpretation of
197 data, in the writing of the report, or in the decision to submit the paper for publication.

198

199 **Results**

200 Between May 2009 and September 2012, 145 subjects (out of 275 subjects screened) were clinically
201 tested for eligibility. The target number of 88 participants was not reached. Seventy-seven subjects
202 were eligible and agreed to participate (Figure 2). Subjects were randomly assigned to either robotic
203 (n = 39) or conventional (n = 38) therapy. The dropout rate was 5%: two participants rejected
204 participation when they were allocated to conventional therapy, one participant developed epileptic
205 seizures during the course of the study and one participant had an accident not related to the study.
206 Seventy-three subjects completed the study with a total of 38 and 35 in the ARMin and the control
207 group, respectively: 13 and 12 in center 1; 11 and 8 in center 2; 5 and 6 in center 3; 9 and 9 in center
208 4; one subject was included in the analysis although he had stopped therapy midway due to medical
209 reasons unrelated to the study, but finished tests ("intention-to-treat"). Eight out of 365 assessments
210 (73 times five assessments) were missed. Three subjects had fewer than 24 therapy sessions (20, 21
211 and 23 therapies, respectively). Two subjects had to be excluded because they had more than 3
212 points difference in the FMA-UE between the tests m1 and t0. Three subjects were included by the
213 evaluators although they exceeded this number (4, 4, and 5 points, respectively) to fulfill the
214 "intention-to-treat" [35]. The subjects' baseline characteristics are summarized in Table 2. Average
215 therapy time per session was 46 minutes (SD \pm 4.0) in the robotic group and 48 minutes (SD \pm 3.7) in
216 the control group.

217

218 **Safety**

219 The participants experienced no serious side effects from the study. Two subjects had minor events
220 relating to the robotic device during the testing procedure: the skin of their arm was bruised leading
221 to flushes of about 1 cm diameter. The device was padded and adjusted, to avoid recurrence of such
222 events. One subject from the ARMin group reported mild shoulder pain; the therapy was interrupted
223 for three sessions and then resumed without further adverse events.

224

225 ***Effects of Therapy***

226 **Primary Outcome**

227 In the FMA-UE, differences between the two treatment groups over the course of the study were
228 significant (FMA-UE: $F = 4.1$, $p = 0.041$, mean difference: 0.78 points, confidence interval, CI [0.03 -
229 1.53], Figure 3). Thirteen out of 38 subjects (34%) in the ARMin group and 9 out of 35 subjects (26%)
230 in the control group gained 5 or more points during therapy (t0 to t2, “responders”).

231 **Secondary Outcomes**

232 Linear mixed models revealed significantly lower gains in mean strength in the ARMin group than in
233 the control group ($F = 5.8$, $p = 0.017$, mean difference: 1.29 Nm, CI [- 2.34 to -0.23], see
234 webappendix). Among the remaining secondary outcomes (SIS, SIS_{pd}, WMFTt, WMFTf, MAL(QOM),
235 GAS, mAS, grip strength) no significant differences between the treatment groups could be revealed
236 (Table 3). For mean strength, normality of residuals in the QQ plot was partly violated and could not
237 be achieved by variable transformation.

Subgroup analysis

When subjects were stratified (applying the median of the respective attributes) according to i) time gap since stroke (< 27 months vs. ≥ 27 months), ii) age (<59 years vs. ≥59 years) or iii) hand dominance (dominant hand affected vs. non-dominant) the outcome was not conclusive regarding changes in motor function. Splitting by iv) severity (<19 points vs. ≥19 points in baseline FMA at t0), a tendency in favor of ARMin over the course of the study could be observed in the more severely affected subjects ($F = 17.36$, $p < 0.001$, mean difference: 1.91 points, CI [1.00 to 2.82], see webappendix).

Discussion

The results of this study confirm that robotic training with ARMin reduces motor impairment with respect to arm and hand function more effectively than conventional therapy. This superiority is based on small absolute differences (0.78 points in the FMA-UE) and a weak significance ($p = .041$) which leave the clinical relevance and evidence in question.

Noteworthy were the gains with robotic therapy in severely affected subjects: it seems that they particularly benefitted from ARMin therapy with a mean difference of 1.91 points in the FMA-UE between the two groups (see also webappendix). These results were acquired in a sub-group analysis. Further studies on severely affected subjects should be conducted before definite conclusions can be drawn.

Intensity of training might be an important factor, though not the only one to favor ARMin. With the robot, task-oriented activities can be trained in 3D-workspace that might be hard to reach during conventional therapy of a severely affected arm; and the patient-cooperative control strategy facilitates the accomplishment of a subject-initiated task.

261 Although the mean gains in the ARMin group averaged 3.25 points in the FMA-UE and were superior
262 to conventional therapy (2.47 points), these changes do not represent clinical relevance with respect
263 to the MCID (about 5 points [23]). Although this MCID was established in subjects with minimal to
264 moderate impairment and does not fully apply to the present target group of moderately to severely
265 affected subjects, it illustrates the challenge to achieve meaningful improvements within the
266 limitations of a clinical study. About one third of the subjects in the ARMin group achieved
267 meaningful gains (increase in FMA-UE ≥ 5 points), against one fourth in the control group. Probably,
268 not all the subjects tapped full potential with only eight weeks of therapy. Although most gains in the
269 robotic group occurred in the first four weeks, subjects improved during the second half of therapy
270 and might have continued so with longer training. A pilot study on robotics had shown that durable
271 and intense treatment facilitated an incremental progression that was necessary for severely
272 affected individuals [36].

273 The results of follow-up tests revealed convergence of both groups, indicating that the robotic group
274 remained fairly stable after therapy while the conventional group continued to improve slightly
275 during the follow-up phases and reached a result similar to that of the robotic group after four weeks
276 therapy (Figure 3). The robotic group gained motor function faster but could not fully consolidate the
277 achievements when the therapy ceased. The results raise the question as to whether the participants
278 in the conventional therapy group learned something that was not reflected in the tests during and
279 immediately after therapy, but useful for further progression during the follow-up. It might be
280 explained by the higher strength gains in the conventional group (see webappendix) which might
281 have enhanced the use of the affected arm in daily life. The present results are in accordance with
282 the findings of the Cochrane meta-analysis [9]: robotic devices may improve paretic arm function,
283 but not arm muscle strength. In the case of ARMin, the parameters for the path assistance might
284 have been chosen too supportive, in this way restraining strength training. Further research should

285 focus on ascertaining if specific strength tasks have to be added to robot therapy to enhance
286 improvement [37].

287 Beside of mean strength, no other secondary outcome measure showed significant differences in
288 favor of either of the two treatments.

289 Due to the nature of an interventional study, participants and therapists are not blinded to group
290 assignment which might erode the validity of the results of a trial. Participants are prone to favor the
291 robotic therapy. In addition, a robotic treatment group might benefit from the incentive of a new
292 therapy. On the other hand, therapists might perceive the robot as a competitor either affecting the
293 way they perform the robotic training or resulting in contamination of the conventional therapy (e.g.
294 by increasing repetition).

295 Several limitations of the study can affect the validity of the results. The eligibility criteria are
296 potentially problematic. We restricted participation in this study to participants in the chronic state
297 to assure that improvement is due to the therapy applied and not to spontaneous recovery.
298 However, this runs the risk that compensation rather than true recovery is the primary mechanism of
299 functional gains [33]. The intended number of 80 participants could not be reached. The achieved
300 sample size of 73 participants was sufficient to detect significant differences for FMA-UE and mean
301 strength. While the FMA-UE did fulfill the model assumptions, some deviation from normality was
302 observed for mean strength. Results for mean strength should hence be treated with caution.

303 More than 70% of participants were engaged in regular rehabilitation (occupational and physical
304 therapies) before entering the study, with an average of more than three sessions weekly. Thus, the
305 full potential might have been already exploited and a therapeutic plateau reached in both groups.

306 In conclusion, we found that neurorehabilitative therapy with task-oriented training, using an
307 exoskeleton robot is safe and can enhance motor recovery of the paretic arm in moderate to severely
308 affected subjects even in the chronic state after stroke. It reduced arm motor impairment more

effectively than did conventional therapy. The mean difference in the FMA-UE was statistically significant but small and is of little clinical relevance for the individual. Both groups gained about three points in the FMA-UE over the course of the study (Figure 3). Plotting the means over time implies that recovery is faster with robot-assisted therapy than with conventional therapy. The ARMin group performed better particularly when we restrict our attention to the severely affected study participants, but these results of post-hoc subgroup-analysis with split sample sizes need caution and further investigation.

That the potential for recovery persists even months after stroke has been verified by several studies [38, 39]. The application of robotic therapy might guide subjects after stroke beyond what is possible with current practice alone.

Formatiert: Englisch (USA)

Competing interests

V. Klamroth-Marganska reports grants from Swiss National Science Foundation and from Bangerter-Rhyner Foundation, during the conduct of the study. In addition, R. Riener and T. Nef are inventors of the patents "System for arm therapy"(WO2008EP08556 20081010) and "System und Verfahren für die kooperative Armtherapie sowie Rotationsmodul dafür" (WO2006058442). ETH Zurich signed a license contract with Hocoma AG (Volketswil, Switzerland), a company which develops and sells rehabilitation robotic devices for treatment of neurological patients. There are no conflicts of interest for J. Blanco, K. Campen, A. Curt, V. Dietz, T. Ettlin, M. Felder, B. Fellinghauer, M. Guidali, A. Kollmar, A. Luft and C. Schuster-Amft.

Authors' contributions

V. Klamroth-Marganska participated in the following aspects of the study: concept and design, coordination, data analysis and interpretation, and manuscript drafting.

332 J. Blanco, K. Campen, T. Ettlin, M. Felder and C. Schuster-Amft participated in the study design and
333 coordination, besides manuscript revision.

334 A. Curt contributed to the design and supervision of the study, data interpretation and manuscript
335 revision.

336 V. Dietz participated in concept and design of the study, temporary supervision of study, and in data
337 interpretation and manuscript revision.

338 B. Fellinghauer and W. Stahel planned the statistical procedures and performed parts of the
339 statistical analyses.

340 M. Guidali contributed to the study design, coordinated parts of the study, helped in data acquisition
341 and manuscript revision.

342 A. Kollmar contributed to the study design and helped in data acquisition and manuscript revision.

343 A. Luft contributed to the study design and was involved in data interpretation and manuscript
344 revision.

345 T. Nef, together with R. Riener, initiated and planned the study concept and design and revised the
346 manuscript.

347 R. Riener headed the project and, together with T. Nef, designed, initiated and planned the study,
348 besides being involved in data interpretation, and drafting and revising the manuscript.

349 All authors have read the final manuscript and gave their approval for its publication.

350

351 **Acknowledgments**

352

353 This work was funded by the Swiss National Science Foundation (Nr.325230-120621) and
354 partly supported by grants of the Bangerter-Rhyner Foundation (project: “ARMin robot”).

355

356 The authors thank the therapists and assessors Ingmar Anner, Joachim Cerny, Andrea Henneke,
357 Daniela Kammerer-Nijman, Barbara Pfahrer, Martin Sattelmayer, Felix Scheiwiller, Olivier Schmid,
358 Mark Schmiedeskamp, and Sabine Schölch for their commitment; Drs. Alexander Duschau-Wicke,
359 Natalia Estevez, Maya Kamber, Francisco Valero-Cuevas, Cordula Werner, Peter Wolf, and Carolee
360 Winstein for invaluable advice; and Dr. Dietmar Heinz for photographs. They convey special thanks to
361 all their patients who kindly participated in this study.

362

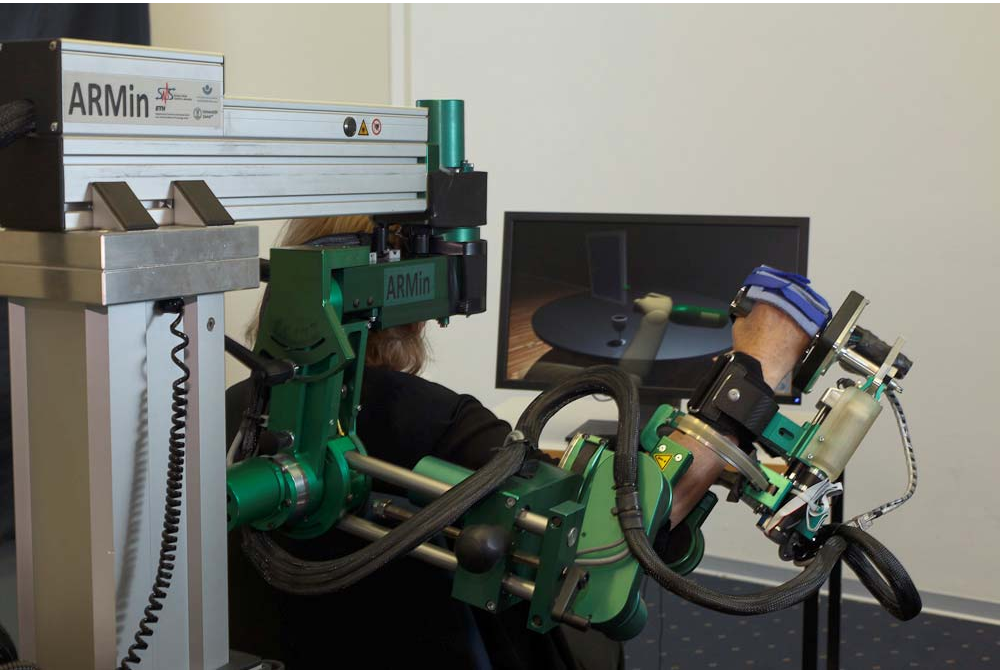
References

- 365 1. Housman SJ, Scott KM, Reinkensmeyer DJ: **A randomized controlled trial of gravity-**
 366 **supported, computer-enhanced arm exercise for individuals with severe hemiparesis.**
 367 *Neurorehabil Neural Repair* 2009, **23**:505-514.
- 368 2. Abdollahi F, Case Lazarro E, Listenberger M, Kenyon R, Kovic M, Bogey R, Hedeker D,
 369 Jovanovic B, Patton J: **Error Augmentation Enhancing Arm Recovery in Individuals With**
 370 **Chronic Stroke: A Randomized Crossover Design.** *Neurorehabil Neural Repair* 2013, **2013**
 371 **Aug 8. [Epub ahead of print.]**
- 372 3. Kim H, Miller LM, Fedulow I, Simkins M, Abrams GM, Byl N, Rosen J: **Kinematic data analysis**
 373 **for post-stroke patients following bilateral versus unilateral rehabilitation with an upper**
 374 **limb wearable robotic system.** *IEEE Trans Neural Syst Rehabil Eng* 2013, **21**:153-164.
- 375 4. **World Health Organization International Classification of Functioning, Disability and**
 376 **Health.** Geneva: World Health Organization <http://www.who.int/classifications/icf/en>.
- 377 5. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford
 378 ES, Fox CS, et al: **Heart disease and stroke statistics--2013 update: a report from the**
 379 **American Heart Association.** *Circulation* 2013, **127**:e6-e245.
- 380 6. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ: **Probability of regaining dexterity in the**
 381 **flaccid upper limb: impact of severity of paresis and time since onset in acute stroke.** *Stroke*
 382 2003, **34**:2181-2186.
- 383 7. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J: **The**
 384 **impact of physical therapy on functional outcomes after stroke: what's the evidence?** *Clin*
 385 *Rehabil* 2004, **18**:833-862.
- 386 8. Brewer BR, McDowell SK, Worthen-Chaudhari LC: **Poststroke upper extremity rehabilitation:**
 387 **a review of robotic systems and clinical results.** *Top Stroke Rehabil* 2007, **14**:22-44.
- 388 9. Mehrholz J, Hädrich A, Platz T, Kugler J, Pohl M: **Electromechanical and robot-assisted arm**
 389 **training for improving generic activities of daily living, arm function, and arm muscle**
 390 **strength after stroke.** *Cochrane Database Syst Rev* 2012, **6**:CD006876.
- 391 10. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, Langhorne P, Price CIM,
 392 Walker A, Watkins CL: **Repetitive Task Training for Improving Functional Ability After**
 393 **Stroke.** *Stroke* 2009.
- 394 11. Kahn LE, Zygmant ML, Rymer WZ, Reinkensmeyer DJ: **Robot-assisted reaching exercise**
 395 **promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled**
 396 **pilot study.** *J Neuroeng Rehabil* 2006, **3**:12.
- 397 12. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, Ringer RJ,
 398 Wagner TH, Krebs HI, Volpe BT, et al: **Robot-assisted therapy for long-term upper-limb**
 399 **impairment after stroke.** *N Engl J Med* 2010, **362**:1772-1783.
- 400 13. Patton JL, Stoykov ME, Kovic M, Mussa-Ivaldi FA: **Evaluation of robotic training forces that**
 401 **either enhance or reduce error in chronic hemiparetic stroke survivors.** *Exp Brain Res* 2006,
 402 **168**:368-383.
- 403 14. Guidali M, Duschau-Wicke A, Broggi S, Klamroth-Marganska V, Nef T, Riener R: **A robotic**
 404 **system to train activities of daily living in a virtual environment.** *Med Biol Eng Comput* 2011,
 405 **49**:1213-1223.

- 406 15. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML: **Computerized arm**
407 **training improves the motor control of the severely affected arm after stroke: a single-**
408 **blinded randomized trial in two centers.** *Stroke* 2005, **36**:1960-1966.
- 409 16. Nef T, Guidali M, Riener R: **ARMin III - arm therapy exoskeleton with an ergonomic shoulder**
410 **actuation.** *Applied Bionics and Biomechanics* 2009, **6**:127-142.
- 411 17. Bayona NA, Bitensky J, Salter K, Teasell R: **The role of task-specific training in rehabilitation**
412 **therapies.** *Top Stroke Rehabil* 2005, **12**:58-65.
- 413 18. Kwakkel G, van Peppen R, Wagenaar RC, Wood Dauphinee S, Richards C, Ashburn A, Miller K,
414 Lincoln N, Partridge C, Wellwood I, Langhorne P: **Effects of augmented exercise therapy time**
415 **after stroke: a meta-analysis.** *Stroke* 2004, **35**:2529-2539.
- 416 19. Lo HS, Xie SQ: **Exoskeleton robots for upper-limb rehabilitation: State of the art and future**
417 **prospects.** *Medical Engineering & Physics* 2012, **34**:261-268.
- 418 20. Langhorne P, Coupar F, Pollock A: **Motor recovery after stroke: a systematic review.** *Lancet*
419 *Neurol* 2009, **8**:741-754.
- 420 21. Dobkin BH: **Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor**
421 **Interventions.** *Neurorehabil Neural Repair* 2009, **23**:197-206.
- 422 22. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S: **The post-stroke hemiplegic patient.**
423 **1. a method for evaluation of physical performance.** *Scand J Rehabil Med* 1975, **7**:13-31.
- 424 23. Page SJ, Fulk GD, Boyne P: **Clinically important differences for the upper-extremity Fugl-**
425 **Meyer Scale in people with minimal to moderate impairment due to chronic stroke.** *Phys*
426 *Ther* 2012, **92**:791-798.
- 427 24. Lin J-H, Hsu M-J, Sheu C-F, Wu T-S, Lin R-T, Chen C-H, Hsieh C-L: **Psychometric comparisons**
428 **of 4 measures for assessing upper-extremity function in people with stroke.** *Phys Ther*
429 2009, **89**:840-850.
- 430 25. Wagner JM, Rhodes JA, Patten C: **Reproducibility and minimal detectable change of three-**
431 **dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke.**
432 *Phys Ther* 2008, **88**:652-663.
- 433 26. Wolf SL, Lecraw DE, Barton LA, Jann BB: **Forced use of hemiplegic upper extremities to**
434 **reverse the effect of learned nonuse among chronic stroke and head-injured patients.** *Exp*
435 *Neurol* 1989, **104**:125-132.
- 436 27. Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E: **Effects of constraint-induced**
437 **movement therapy on patients with chronic motor deficits after stroke: a replication.**
438 *Stroke* 1999, **30**:586-592.
- 439 28. Uswatte G, Taub E, Morris D, Light K, Thompson PA: **The Motor Activity Log-28: assessing**
440 **daily use of the hemiparetic arm after stroke.** *Neurology* 2006, **67**:1189-1194.
- 441 29. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ: **The stroke impact scale**
442 **version 2.0. Evaluation of reliability, validity, and sensitivity to change.** *Stroke* 1999,
443 **30**:2131-2140.
- 444 30. Kiresuk TJ, Lund SH, Larsen NE: **Measurement of goal attainment in clinical and health care**
445 **programs.** *Drug Intell Clin Pharm* 1982, **16**:145-153.
- 446 31. Bohannon RW, Smith MB: **Interrater reliability of a modified Ashworth scale of muscle**
447 **spasticity.** *Phys Ther* 1987, **67**:206-207.
- 448 32. **Research Randomizer** [<http://www.randomizer.org>]
- 449 33. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos, Machiel: **Robot-assisted**
450 **movement training compared with conventional therapy techniques for the rehabilitation**
451 **of upper-limb motor function after stroke.** *Arch Phys Med Rehabil* 2002, **83**:952-959.
- 452 34. Zielhuis GA HP, Maltha JC van Riel PL: *Handleiding medisch-wetenschappelijk onderzoek.*
453 1995.
- 454 35. Hollis S, Campbell F: **What is meant by intention to treat analysis? Survey of published**
455 **randomised controlled trials.** *BMJ* 1999, **319**:670-674.

456 36. Daly JJ, Hogan N, Perepezko EM, Krebs HI, Rogers JM, Goyal KS, Dohring ME, Fredrickson E,
 457 Nethery J, Ruff RL: **Response to upper-limb robotics and functional neuromuscular**
 458 **stimulation following stroke.** *J Rehabil Res Dev* 2005, **42**:723-736.
 459 37. Patten C, Lexell J, Brown HE: **Weakness and strength training in persons with poststroke**
 460 **hemiplegia: rationale, method, and efficacy.** *J Rehabil Res Dev* 2004, **41**:293-312.
 461 38. Ferrarello F, Baccini M, Rinaldi LA, Cavallini MC, Mossello E, Masotti G, Marchionni N, Di Bari
 462 M: **Efficacy of physiotherapy interventions late after stroke: a meta-analysis.** *J Neurol*
 463 *Neurosurg Psychiatry* 2011, **82**:136-143.
 464 39. Page SJ, Gater DR, Bach YRP: **Reconsidering the motor recovery plateau in stroke**
 465 **rehabilitation.** *Arch Phys Med Rehabil* 2004, **85**:1377-1381.

466



467

468 **Figure 1** Subject performing task-oriented training (filling a glass) with ARMin

469 **Table 1** Eligibility criteria for participation in the study

Diagnosis of a single, first ever cerebrovascular accident (CVA) verified by brain imaging (magnetic resonance imaging [MRI] or computer tomography [CT])
Chronic stage after stroke (minimum six months)
Moderate to severe arm paresis, as indicated by a score of 8 to 38 out of the maximum 66 points in the FMA-UE

Minimum age 18 years
Stable recovery stage
Able to sit in a chair without any additional support and without leaning on the back rest
Passive range of motion (pROM) in the shoulder: anteversion/retroversion 80°/0°/20°, abduction/adduction 60°/0°/10°, inner and outer rotation 20°/0°/20°; in the elbow: flexion/extension 100°/40°/40°
No excessive spasticity of the affected arm (modified Ashworth Scale mAS ≤ 3 out of 0-5)
No serious medical or psychiatric illness
No participation in any clinical investigation within four weeks prior to the start of this study
No participation in any therapeutic treatment (outside therapy) performed with the paretic arm during the therapy phase of the study
No anticipated need for any major surgery during the study
No pregnancy or breast feeding (for women subjects); no orthopedic, rheumatologic or other disease restricting movements of the paretic upper extremity
No shoulder subluxation (palpatory < 2 fingers)
No skin ulcerations at the paretic arm
Ability to communicate effectively with the examiner such that the validity of the patient's data could not be compromised
No cybersickness
No pace-maker or other implanted electric devices
Body weight lower than 120kg
No serious cognitive defects or aphasia preventing the performance of the ARMin treatment

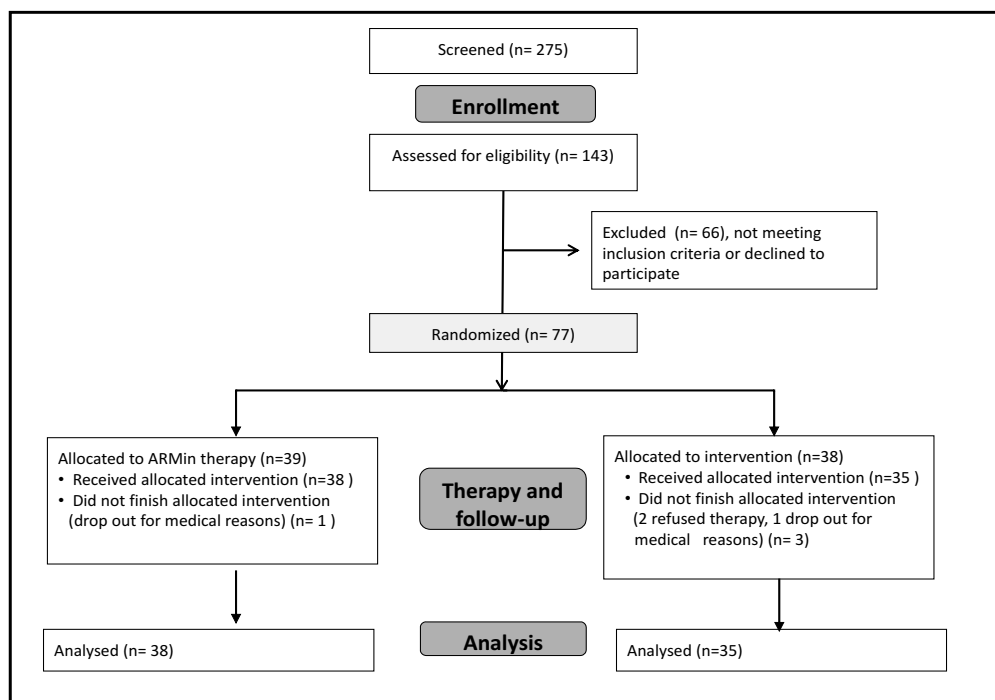


Figure 2 Flow diagram of study enrollment and completion

473 Table 2 **Baseline characteristics of participating subjects. FMA-UE: Fugl-Meyer Assessment (upper**
474 **extremity motor function); WMFT: Wolf Motor Function Test; MAL-QOM: Motor Activity Log,**
475 **quality of movement; SIS = Stroke Impact Scale.**

	ARMin		control	
	N	Mean \pm SD (min – max)	N	Mean \pm SD (min – max)
Age in years at therapy	38	55 \pm 13 (22 – 75)	35	58 \pm 14 (27 – 76)
Months since stroke	38	52 \pm 44 (7 – 171)	35	40 \pm 45 (7 – 168)
Gender				
Female	17		10	
Male	21		25	
N with additional therapy	20		23	
Hours per week	30	1.6 \pm 1.7 (0 -6)	34	1.8 \pm 1.8 (0 – 6)
Total therapy hours	30	2.2 \pm 2.2 (0 – 9)	34	2.2 \pm 2.1 (0 – 8)
Physiotherapy	30	1.0 \pm 1.0 (0 – 3)	34	1.0 \pm 0.9 (0 – 3)
Occupational therapy	30	0.7 \pm 0.9 (0 – 3)	34	0.8 \pm 0.9 (0 – 3)
FMA-UE baseline	38	20.2 \pm 7.1 (8 – 36)	35	20.7 \pm 8.2 (8 – 37)
WMFT function	38	2.0 \pm 0.8 (0.7 – 3.3)	35	2.0 \pm 0.6 (0.8 – 3.9)
WMFT time	38	67 \pm 23 (22 – 114)	35	65 \pm 29 (3 – 112)
MAL-QOM	38	0.8 \pm 0.6 (0 – 2.3)	35	0.8 \pm 0.6 (0.1 – 2.3)
SIS total	38	64 \pm 11 (41 – 83)	35	62 \pm 11 (31 – 81)
SIS physical domain	38	53 \pm 13 (21 – 81)	35	52 \pm 13 (24 – 72)
mAS	38	0.8 \pm 0.4 (0.0-1.8)	35	0.6 \pm 0.4 (0.0-1.8)
Mean strength (Nm)	38	10 \pm 8 (0 – 32)	35	11 \pm 7.6 (0 – 29)
Grip strength	38	5.0 \pm 4.8 (0 – 19)	35	5.6 \pm 4.7 (0 – 18)
FMA-UE baseline \geq 19	22	25 \pm 5 (19-36)	17	27 \pm 6 (19-37)
FMA-UE baseline <19	16	14 \pm 3 (8-18)	18	15 \pm 3 (8-18)
FMA-UE in subjects with months since stroke <27	21	20.3 \pm 6.8 (8-36)	15	21.4 \pm 9.7 (9-37)
FMA-UE in subjects with months since stroke \geq 27	17	20.2 \pm 7.6 (9-34)	20	20.3 \pm 7.1 (8-37)
Age < 59 years	19	45 \pm 9.9 (22-56)	16	46 \pm 9.4 (27-57)
Age \geq 59 years	19	66 \pm 5 (59-75)	19	69 \pm 5 (59-76)
Months since stroke <27	17	18 \pm 6 (7-26)	20	13 \pm 6 (7-25)
Months since stroke \geq 27	21	80 \pm 42 (28-171)	15	76 \pm 48 (29-168)
Hand dominance/ impaired side				
Left/left	2		0	
Right/left	17		19	
Right/right	17		15	

Left/right	2	1
Dominant side affected	19	15

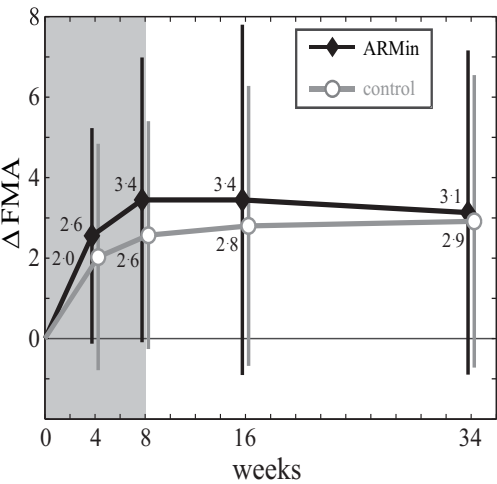


Figure 3 Change in FMA-UE as compared to baseline during the course of study - a comparison between conventional (control) and robotic therapy groups (ARMin); Error bars are standard deviations.

Table 3 F-ratios,significance levels, estimated marginal means, and confidence intervals for primary and secondary outcomes. CI: confidence interval; FMA-UE: Fugl-Meyer Assessment (upper extremity motor function); WMFT: Wolf Motor Function Test: MAL-QOM: Motor Activity Log, quality of movement; SIS = Stroke Impact Scale, mAS = modified Ashworth Scale; GAS = Goal Attainment Scale.

group effect				
	F-ratio	p value	estimated marginal means	CI
FMA-UE	4.2	.041	0.78	0.03 to 1.53
WMFT time	1.4	.173	2.02	-0.90 to 4.93
WMFT function	1.6	.212	-0.37	-0.10 to 0.021
SIS total	3.6	.059	1.42	-0.05 to 2.91
SIS physical domain	0.8	.387	0.76	-0.96 to 2.47

MAL-QOM	·1	·751	0·13	-0·07 to 0·10
mAS	3·0	·083	-0·62	-0·13 to 0·01
GAS	3·23	·077	-0·39	-0·82 to 0·04
Mean strength	5·7	·017	-1·29	-2·34 to - 0·23
Grip strength	1·7	·196	-0·41	-1·04 to 0·21

489

490

491

Research in context:

492

We searched Medline (1950 till October 16, 2013) and Google Scholar for articles published in any language with the search terms “stroke”, “robot”, “randomized” or “randomised”, “clinical trial”, “exoskeleton” or “exoskeletal”, “upper limb” or “upper extremity” or “arm”, and “task-oriented”. We obtained 209 articles. After visual inspection we included all RCT’s focusing on upper limb rehabilitation training with a robotic exoskeleton device that allows task-specific training. This inspection resulted in three publications. Two RCT [1, 2] reported about therapy results with the T-WREX system, a passive 5 degree-of-freedom arm orthosis that contains no robotic actuation but offers variable levels of gravity support. One study with an exoskeleton robot (UL-EXO7)[3] reported a RCT, where 15 subjects were randomly assigned to either bilateral UL-EXO7 training, unilateral UL-EXO7 training, or usual care. However, in this publication, only the two robotic training groups were reported but not the control group (usual care).

The search confirmed that no RCT on exoskeleton robots had been published.

Interpretation:

The present RCT study is the first one that compares upper limb rehabilitation training with a robotic exoskeleton device with conventional therapy in chronic post-stroke subjects. The results indicate that robotic training of the affected arm with the ARMin exoskeleton reduces impairment and enhances arm motor function more effectively than conventional therapy.